Appendixes

A

Abstracts of Commissioned Papers

Approaches for the Collection and Use of Personal Exposure and Human Biological-Marker Information for Assessing Risks to Deployed U.S. Forces

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Abstract

Risk management is especially important for military forces deployed in hostile or chemically contaminated environments. On-line communications or rapid turnaround capabilities for assessing exposures can create viable options for preventing or minimizing incapacitating exposures or latent disease or disability in the years after the deployment. With military support for the development, testing, and validation of state-of-the-art personal and area sensors, telecommunications, and data management resources, the Department of Defense can (1) enhance its capabilities for meeting its novel and challenging tasks and (2) create technologies that will find widespread civilian uses.

This paper assesses currently available options and technologies for productive pre-deployment environmental surveillance, exposure surveillance during deployments, and retrospective post-deployment exposure surveillance. It introduces some opportunities for technological and operational advancements in technology for more effective exposure surveillance and effects management options for force deployments in future years. The issues discussed include: (1) information needs for assessing

personal exposures and risks for deployed forces; (2) options for pre-deployment baseline determinations, for collection of personal exposure-related data during field deployment, and for post-deployment personal exposure assessments; (3) maximizing effective personal exposure data resources during deployment and post-deployment; (4) technical capabilities for personal exposure assessment; and (5) assessing risks.

Advances in information technology have made it possible to envision the collection, maintenance, and utilization of deployment data that would enable theater commanders and medical staff to recognize and evaluate environmental health hazards and to manage deployments to avoid or minimize those hazards. Such data, together with a deployment sample archive, would also facilitate future epidemiological studies that could identify additional causal relationships between environmental factors and health outcomes.

Applications can include: (1) on-line communications access to remote sensing devices and continuous monitoring of data for tactical planning; (2) data review by medical staff personnel to determine the need for monitoring military personnel for possible effects of toxic exposures, provide countermeasures during deployments, and set priorities for medical examinations and biomarker sample collections and analyses in the early post-deployment period; (3) additional sampling or monitoring, or analysis of archived samples, to resolve ambiguities or conflicts concerning levels of exposure or environmental contamination; and (4) post-deployment review of medical and environmental data by epidemiologists in investigations of possible causal factors for delayed illness reports associated with service in a specific deployment.

Each of these applications could consume large amounts of resources, and the allocations should be decided according to pre-established priorities by an appropriate panel of peers, including military users and state-of-the-art research investigators with expertise in the emerging technologies.

Characteristics of the Future Battlefield and Deployment

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Abstract

In an era of unprecedented change, the military planner of today must prepare for contingencies involving operations by forces of a very large size to forces for special operations and operations other than war that might involve just a few soldiers, sailors, or airmen. The entire spectrum of geographical features and weather conditions must be accounted

for in the plan. The typical linear battlefield will be replaced by a combat situation with a 360-degree threat, the potential for new high-technology weapons, the use of chemical and biological agents, and the use of nontraditional forces and terrorism.

With the gradual urbanization of the world's population, future battles will inevitably be fought within city limits geometrically compounding the planner's problem and the force commander's options. In addition to the threat from the opposing force, the field commander will face structural damage, local industrial hazards, and loss of mobility and degradation of communication links.

Combined, the future battlefield and force deployment scenarios will, in spite of extensive training, provide for extremely high levels of stress. The threats from emerging bacteria and viruses, chemical weapons and industrial compounds, and the urban battlefield will additionally inhibit and stress combat forces. Changes in force structure, national demographics, and the greater reliance on women in combat roles will require minimal changes in force protection.

Natural disease or disease from biological or chemical weapons, nonbattle injury, including industrial-hazard exposure, and stress will continue to be the major threats to deployed forces in the future. Military and industrial intelligence of contested areas, modern equipment, extensive training, and pre- and post-deployment health studies will provide the most successful means of force protection.

The Nature of Risk Assessment and its Application to Deployed Forces

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Abstract

An analytical framework applicable to the assessment of the wide range of risks to health and safety potentially encountered by U.S. forces deployed to unfamiliar environments is presented as a guide to experts involved in the evaluation of diverse information on specific hazards. Adherence to the guidance should ensure that risk assessment results are clearly and consistently presented, and that they are suitable for practical, risk-management decision-making. The analytical framework presented is that first described by the National Research Council (NRC) (1983) and long in use for assessing risks of hazardous conditions, substances, and agents (referred to collectively as "stressors"). This paper attempts to describe how the analytical framework can be applied in diverse situa-

tions, and to many types of stressors, such as pathogens, toxic chemicals, and physical hazards. The framework for risk assessment, as originally conceived by the NRC, is a guide to the organization and evaluation of information and its attendant uncertainties, and does not require specific methodological approaches; the methodologies used should be those appropriate to the relevant scientific disciplines (e.g., toxicology, microbiology). The framework offered in the paper includes a means for reduction of complex information to usable formats. It recognizes that the purpose of the risk-assessment process is *not* to set standards that can be used for "yes-no" decision-making. Rather, in the current context, its purpose is to allow the Department of Defense decision-makers sufficient information to examine a range of risks that might arise in rapidly changing deployment conditions, and to balance competing risks so that overall risks to deployed forces can be minimized.

Future Health Assessment and Risk Management Integration for Infectious Diseases and Biological Weapons for Deployed U.S. Forces

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Abstract

The health of the United States armed forces has been viewed as a critical component of the strength, readiness, and effectiveness of the military's ability to meet various degrees of threats to peace, human rights abuses, and other global disasters in the United States and the world. Compared with any other country or entity in the world, the U.S. military has one of the best surveillance and monitoring systems for assessing the risk of infectious disease globally. The monitoring is broad-based, specific for a large list of pathogenic agents, but includes generic symptomology that might be due to a multitude of current, emerging, or reemerging microorganisms; the monitoring is also timely. Gastrointestinal illness and respiratory and skin infections remain a problem for deployed troops.

It is now well known that microbial infections can result in chronic outcomes associated with heart, neurological, and immunological disorders. Therefore, hospitalization data will no longer suffice as the sole measure of severity and lost effectiveness to the troop force at large. Better assessment of antibiotic-resistant bacteria, coxsackieviruses, and *Legionella* and an evaluation of the underdiagnosis and underreporting of protozoa such as *Cryptosporidium* are needed. New microorganisms are being reported every year that might be associated with many of these illnesses,

and prospective surveillance might be needed using new techniques to better understand the infection rates and asymptomatic infections.

Risk-assessment methods can now be used to quantify the risk of microbial infections and to address exposure and potential outcome from naturally occurring microorganisms and biological weapons. Hazard identification includes the identification of the microbial agent as well as the spectrum of human illnesses ranging from asymptomatic infections to death. The host response to the microorganisms with regard to immunity and multiple exposures should be addressed here, as well as the adequacy of animal models for studying human impacts. Endemic and epidemic disease investigations, case studies, hospitalization studies, and other epidemiological data are needed to complete this step in the risk assessment. The variables need to be carefully defined and the data quantified as ratios. The dose-response assessment is the mathematical characterization of the relationship between the dose administered and the probability of infection or disease in the exposed population. Dose-response assessments have been referred to as probability-of-infection models, which are developed from mostly human volunteer studies. The exposure assessment determines the size and nature of the population exposed, the route, concentrations, and distribution of the microorganisms, and the duration of the exposure. The description of exposure includes not only occurrence based on concentrations but also the prevalence (how often the microorganisms are found) and distribution of microorganisms in space and over time. Exposure assessment is determined through occurrence monitoring and predictive microbiology. Quantitative risk characterization should estimate the magnitude of the public health problem, and demonstrate the variability and uncertainty of the hazard, using four distributions: (1) the spectrum of health outcomes; (2) the confidence limits surrounding the dose-response model; (3) the distribution of the occurrence of the microorganism; and (4) the exposure distribution. Assessments of occurrence and exposure can be further delineated by distributions surrounding the method of recovery and survival (treatment) distributions.

The risk-assessment framework already fits into the Department of Defense's (DOD's) programs associated with risk management. The critical need will be the development of databases that can be used in the decision and management process. Although health outcomes and morbidity and mortality statistics are available from numerous databases and surveillance programs, the data lacking are often the long-term assessments and chronic outcomes. The exposure assessment, particularly during deployment, is more suspect to uncertainty, especially in terms of quantitative evaluations. Geographic, climatic, seasonal, dose-response, and exposure scenarios can be used to develop tools for setting priorities

for assessment of pre-deployment risks. Risk models can be evaluated for plausibility during outbreak investigations or disease surveillance operations. Exposure and health outcomes must be better assessed.

The use of quantitative assessments allows one to begin to build exposure scenarios in which thresholds associated with ineffectiveness in the troops in a given time frame can be determined for specific agents. For biological weapons, dose-response models should be developed and time and concentration exposure and consequence scenarios should be built and evaluated.

Finally, the formal expansion of DOD's mission on emerging infectious diseases in June 1996 by Presidential Decision Directive NSTC-7 now includes global surveillance, training, research, and response. One of the major assets in implementing this new directive is the overseas research laboratory system that is currently in place: the DOD Infectious Disease Research Laboratories. At a minimum, each laboratory staff should be trained in risk-assessment methods, should have molecular capabilities (polymerase chain reaction [PCR]), and be trained in the use of the global information system (GIS) for maintaining and analyzing the databases.

Approaches for Using Toxicokinetic Information in Assessing Risk to Deployed U.S. Forces

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Abstract

If there is no exposure, there is no toxicity. If there is exposure, toxicity might ensue when exposure exceeds a certain dose or time, a topic discussed under toxicokinetics and toxicodynamics. Analysis of the fundamental equation of toxicity yields the recognition of three independent time scales. One is the dynamic time scale, which is an intrinsic property of a given compound (what does a chemical do to an organism). The second is the kinetic time scale, which is an intrinsic property of a specific organism (what does an organism do to a chemical). The frequency of exposure denotes the third time scale, which is independent of dose and of the dynamic and kinetic time scales. Frequency of exposure depends on the experimental design or nature, but not on the organism or substance. A liminal condition occurs when the frequency becomes infinite, which corresponds to continuous exposure. Continuous exposure forces the dynamic and kinetic time scales to become synchronized, thereby reducing complexity to three variables: dose, effect, and one time scale.

Keeping one of those variables constant allows one to study the other two variables reproducibly under isoeffective, isodosic, or isotemporal conditions. However, any departure from continuous exposure will introduce the full complexity of four independent variables (dose, and the kinetic, dynamic, and frequency time scales) impacting on the effect (dependent variable) at the same time. The examples discussed in this paper demonstrate how nature in the form of long half-lives provides liminal conditions when either kinetic or dynamic half-lives force synchronization of all three time scales.

The original charge for this paper was to conceptualize the role of toxicokinetics in the risk assessment of deployed forces exposed to chemicals. Most toxicologists familiar with current trends in toxicology are aware of the tremendous proliferation of publications combining physiologically based pharmacokinetic (PBPK) models with various dose-response extrapolation models, usually with the linearized multistage (LMS) model, or more recently with the benchmark (BM) curve-fitting approach. This author has used both PBPK and classical pharmacokinetics in many experiments. Although both are conceptually sound, there is one fundamental difference: classical pharmacokinetics uses time as an explicit function, whereas PBPK deals with time mostly as a variable, to be predicted based on physiological and physicochemical parameters. Therefore, the concepts of classical pharmacokinetics were helpful in the development of the initial core of a theory of toxicology, as presented in this document, whereas the concepts of PBPK were not as useful. This is not to say that combining PBPK with a theoretically sound biological model will not provide appropriate answers in some instances. However, as long as PBPK is used in conjunction with biologically implausible models (LMS, BM), it will lead (not surprisingly) to insignificant improvements. Central to the development of the concepts presented here was the notion that time is a variable equivalent to dose in toxicology. This idea has been around among toxicologists for almost exactly 100 years. Nevertheless, claims of exceptions to this idea as embodied in Haber's Rule prevented the development of time as a variable of toxicity. Even today toxicologists tend to focus on the so-called "exceptions" when effects are overwhelmingly dose—but not time—dependent. They do not realize that they are studying extreme parts of a spectrum under liminal conditions (e.g., a highly reversible effect on a short time scale), and they use experimental models with insufficient time resolution. When time resolution is satisfactory (such as pungency on a scale of seconds), clear summation effects emerge.

Recognition of the limits of the current risk-assessment paradigm made a paradox clear: none of the current risk projections include time as a variable even though any and all such risk predictions are by definition

made in time. From this recognition it was concluded that something that is basically flawed cannot be fixed. Therefore, a new risk-assessment paradigm that includes time as a variable of toxicity, is being suggested. It is clear that although dose is a simple function (number of molecules), time is a complex variable, which runs on many different scales, at least three of which are interacting with dose to provide the complexity that seems to have bewildered generations of toxicologists. The three time scales are the toxicokinetic and toxicodynamic half-lives and the frequency of exposure. Thus, there are three liminal conditions:

1. When the toxicokinetic half-life is very long, it keeps the frequency of exposure essentially infinite (continuous exposure), and the toxicodynamic half-life by definition will be the same as the toxicokinetic one. Under these liminal conditions, $c \times t = k$ for isoeffective experiments, because there is only dose-dependence and one time-dependence.
2. When the toxicodynamic half-life is very long, it requires no additional injury to occur to keep injury constant nor the continuous presence of the noxious agent to result under isoeffective conditions in $c \times t = k$, because there is only dose- dependence and one time-dependence.
3. When the toxicokinetic/toxicodynamic half-lives become very short, they will blur the distinction between the kinetic and dynamic time scales and both will become less important, because in that case the frequency of exposure dominates the time-dependence. Under liminal (continuous exposure = infinite frequency) and isoeffective conditions, this will also lead to $c \times t = k$.

When experiments are conducted under isodosic or isotemporal conditions, then the relationship will obey the equation $c \times t = k \times \mathit{Effect}$. The vast majority of exposure scenarios are of course far from these liminal situations (ideal conditions) and will, therefore, yield $c \times t^x = k$. There are clear suggestions in this paper for the type of experiments that need to be done to determine x with exactitude. In the meantime, practical suggestions are included, which illustrate how to use a decision tree or available databases to conduct risk assessments for deployment situations that are less arbitrary by using both dose and time as variables of toxicity.

The decision tree approach uses a top-to-bottom analysis of identifying rate-determining or rate-limiting steps in the toxic action of a given compound for a specific effect. The advantage of this approach is its flexibility of determining at what level to contemplate modeling (risk assessment) of toxicity without having to rely on default assumptions. As recognized by other scientific disciplines, understanding of complexity is always advanced at three levels of investigations: experimental, computational, and theoretical. For the most part, toxicologists were and are

engaged in experimental and computational studies with very little, if any, progress having been made in developing a comprehensive theory of toxicology. The combined theory and decision-tree analysis presented here should allow rapid progress in improving predictions of toxicity, if experimental design, computational goal, and theory come into equilibrium in terms of checks and balances. Instead of claiming exceptions, the three questions to be asked should be:

1. Why do some experimental results deviate from $c \times t = k$ (iso-effective) or $c \times t = k \times Effect$ (isodosic, isotemporal)?
2. What kind of computational (modeling) approach, and what level of integration, is needed to transform $c \times t^x = k$ or $c \times t^x = k \times Effect$ back to $c \times t = k$ or $c \times t = k \times Effect$?
3. How does exploration of Questions 1 and 2 improve the theory of toxicology, specifically the understanding of k?

It must be recognized that eventually experiments will be conducted under ideal conditions $c \times t = k$ or $c \times t = k \times Effect$). Once it is known how to transform $c \times t^x = k$ or $c \times t^x = k \times Effect$ (real-life situations) back to the ideal conditions, then any projection will also be possible in the opposite direction. Thus, it can be expected that the vast majority of experiments conducted under less-than-ideal conditions will then become interpretable by using a related study, which has been conducted under ideal conditions.

Health Risks and Preventive Research Strategy for Deployed U.S. Forces from Toxicologic Interactions Among Potentially Harmful Agents

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Abstract

The goal of this paper is to recommend to the Department of Defense (DOD) a preventive research strategy for deployed U.S. forces to prevent future illness from toxicological interactions from potentially harmful agents. By doing so, it is implicit that potential health risks exist in deployments because of possible exposures to multiple chemicals, drugs, and biologics under stressful environmental and occupational conditions similar to those in the Persian Gulf War. This conclusion was reached based on the author's knowledge of toxicological interactions among chemicals and other agents and his assessment of the available literature information to date. It should be emphasized that this is not an effort to

provide an exhaustive review of the field of toxicological interactions of chemical mixtures and other stressors. In fact, some of the areas are so new that the knowledge base is embryonic at best. DOD, through the National Research Council (NRC), seeks expert advice because of the limited information in the area of adverse health effects resulting from multiple stressors, including exposure to chemical mixtures, drug mixtures, vaccine mixtures, and physical and biological agents under highly stressful and hazardous environmental and occupational conditions. Furthermore, psychological stress undoubtedly plays a role in the potential development of such adverse health effects. There is probably no one individual or any group of individuals who knows the answers to such complex situations. Therefore, the author's opinions are, in some cases, based on educated guesses.

Given the principal goal stated above, this paper:

(1) Discusses the current thinking on toxicological interactions at low-exposure doses, principally to chemicals. However, known and potential toxicological interactions involving biological and physical agents, as well as stressful environmental conditions, are also discussed.

(2) Provides an assessment based on experimental toxicological studies of the effects of agents known to be present in the Persian Gulf War. The concerns about the surprising toxicological interactions discovered after the Persian Gulf War are discussed. These new discoveries offer potential explanations for the Gulf War Syndrome.

(3) Illustrates the importance of the mechanistic understanding of the disease process through research by summarizing some of the studies reported in the literature, which offers a possible explanation for the neurotoxicities of the Gulf War Syndrome.

(4) Looks into the rediscovered area of hormesis, as well as the little-known area of multiple stressors. Their potential roles in the field of toxicological interactions are discussed.

(5) Explains genetic polymorphism as a basis for sensitive populations. A specific example in experimental toxicology involving multiple stressors is given as an illustration.

(6) Offers a preventive research strategy to DOD to avoid possible future Gulf War Illnesses in deployed forces. The rationale, significance, and how-to's for such a preventive research strategy are given in detail.

(7) Discusses the ongoing and possible future development of predictive tools for toxicological interactions among chemicals, drugs, biologics, physical and biological agents, and other multiple stressors. Philosophical issues and future perspectives in the context of the present task are also discussed.